REMARKS

In a non-final Office Action dated July 5, 2007, the Examiner objected to the Specification and rejected Claims 1-17 under 35 U.S.C. §§ 112, 103 and 101.

Applicants respond to the Examiner's objection and rejections below. In view of the amendments noted above and the remarks presented herein, Applicants respectfully request reconsideration of the merits of this application. Accordingly, Applicants respectfully request that a timely notice of allowance be issued in this case.

Restriction Requirement

On March 8, 2007, one of Applicants' representatives, Jean C. Baker, elected Group I (Claims 1-17) in a Response to Requirement for Restriction. The Examiner made the restriction final. Consequently, Claims 18-23 are hereby withdrawn from prosecution.

Objections to Specification

The Examiner objected to paragraph [0002] as unclear for being blank. Paragraph [0002] is the Statement Regarding Federally Sponsored Research or Development, and recites "--" to indicate that the invention was made without United States government support. To clarify this point, Applicants amend paragraph [0002] to recite "Not applicable."

The Examiner also objected to paragraph [0006] for having a typographical error. Applicants amend paragraph [0006] so that "tNRA" is now "tRNA." In view of these amendments, Applicants respectfully request reconsideration of these objections as applied to the Specification.

Rejections Under 35 U.S.C. § 112, second paragraph

The Examiner rejected Claims 1-17 under 35 U.S.C. § 112, second paragraph, as indefinite. The Examiner alleged that Claim 1 is unclear and ambiguous as to how a target RNA molecule can comprise a bulge-helix-bulge (BHB) conformation, but not comprise a tRNA structure (*i.e.*, (1) a 5'-terminal phosphate group; (2) an acceptor stem comprising a seven base pair stem made by the base pairing of the 5'-terminal nucleotides with the 3'-terminal nucleotides; (3) a CCA tail at the 3' end; (4) a D loop comprising a four base pair stem ending in a loop; (5) an anticodon loop comprising a five base pair stem whose loop contains the

anticodon; and (6) a T loop comprising a five base pair stem, as shown in FIGS. 1A-B). Applicants respectfully disagree.

One of ordinary skill in the art understands that RNA, by virtue of its ability to base pair with itself or by virtue of its ability to base pair with a second nucleic acid molecule, can form a BHB, independent of any other tRNA structure. *See, e.g.*, paragraph [0038] of the application; *see also*, FIGS. 4-5, 7A, 8, 9A, 10, 11A-B, 13 and 16-17 of the application. In addition, paragraph [0035] of the application provides one of ordinary skill in the art with guidance as to the structure of the BHB, as it discloses that the structural elements of the BHB are "an RNA bulge on one strand, a 4 base pair helix, and an RNA bulge of the opposite strand. The bulges are typically 3 nucleotides in length." *See also*, paragraphs [0063] and [00119] of the application. As such, the application, along with the knowledge possessed by one of ordinary skill in the art, provides more than adequate detail as to how a target RNA can comprise a bulge-helix-bulge (BHB) conformation, but not comprise a tRNA structure.

In an effort to clarify the distinction between the target molecule and tRNA molecules in general, Applicants amend Claims 1 and 12 to recite that the target RNA is a "non-tRNA" target RNA. Support for this amendment is located in paragraph [0062] of the application. In view of the amendments noted above and the remarks presented herein, Applicants respectfully request reconsideration of this rejection as applied to Claims 1 and 12, as well as the claims that depend therefrom.

Rejections Under 35 U.S.C. § 112, first paragraph

The Examiner rejected Claims 1-17 under 35 U.S.C. § 112, first paragraph, for failing to comply with the written description requirement. The Examiner alleged that the application does not allow one of ordinary skill in the art to use a tRNA endonuclease to cleave a non-tRNA target RNA complexed with another oligonucleotide to form a BHB because the application describes a single example of such cleavage -- mouse profilin 1 mRNA. Applicants respectfully disagree.

The application discloses that non-tRNA target RNA can be cleaved by eukaryal endonucleases when the BHB is present in cis or in trans. As noted by the Examiner, one example of cleavage when the BHB is in trans was mouse profilin 1. *See* Example 2 and FIG. 3. However, the application notes that what is most important is the structural features of the BHB,

which the application describes as an RNA bulge on one strand, a four base pair helix, and an RNA bulge of the opposite strand, where the bulges are typically three nucleotides in length. More importantly, the application discloses that the conformation of the BHB is more important than the sequence. *See*, paragraph [00120] of the application, as well as the FIGS, especially FIGS. 4 and 13. Applicants submit that one of ordinary skill in the art is more than capable of constructing BHBs in trans when presented with any sequence given what one of ordinary skill in the art knows about Watson-Crick base pairing and even oligonucleotide primer design. As such, the application provides more than adequate guidance for one of ordinary skill in the art to cleave any RNA molecule having a BHB constructed in trans.

In an effort to clarify the structure required for forming a BHB between two RNA molecules, Applicants amend Claims 1 and 12 to recite that one bulge of the BHB has a guanine/adenine dinucleotide and the other bulge of the BHB has an either an uracil/adenine dinucleotide or a thymine/adenine dinucletide. Support for this amendment is located in, *e.g.*, FIGS. 1(4), 5, 8, 14A In view of these remarks, Applicants respectfully requests reconsideration of this rejection as applied to Claims 1-17.

Rejections Under 35 U.S.C. § 103

The Examiner rejected Claims 1-17 as obvious over Fabbri S, *et al.*, "Conservation of substrate recognition mechanisms by tRNA splicing endonucleases," Science 280:284-286 (1998) in view of Santoro S & Joyce G, "A general purpose RNA-cleaving DNA enzyme," Proc. Natl. Acad. Sci. USA 94:4262-4266 (1997). The Examiner alleged that it would have been obvious to one of one or ordinary skill in the art to use the BHB motif-mediated cleavage activity of tRNA endonucleases of Fabbri *et al.* in a method of cleaving a target RNA sequence after reading Santoro & Joyce. Applicants respectfully disagree.

With respect to Claims 1-11, Fabbri *et al.* disclosed that eukaryal tRNA endonucleases can process pre-tRNAs having a BHB, which is a structure used by archaeal endonucleases for processing pre-tRNAs. In addition, Fabbri *et al.* emphasized the importance of pre-tRNA secondary structure in the target RNA molecule (*see, e.g.*, FIG. 1), but it did not contemplate or disclose that eukaryal tRNA endonucleases could cleave non-tRNA molecules. The pending claims, however, specifically recite that the target RNA molecule does not comprise a tRNA structure. Moreover, Applicants amend Claim 1 to recite that the BHB is obtained by

hybridizing the target RNA with an oligonucleotide designed to form a BHB (*i.e.*, a trans-formed BHB). Fabbri *et al.* did not contemplate or disclose trans-formed BHBs.

Santoro & Joyce disclosed that its DNAzymes can cleave a substrate at either an AG or AU (FIG. 2). DNAzymes are catalytic nucleotides and are therefore not structurally the same as eukaryal tRNA endonucleases, which are protein enzymes that are comprised of amino acids. While catalytic nucleotides recognize substrates based upon Watson-Crick base pairing, tRNA endonucleases do not. Instead, eukaryal tRNA endonucleases, like all protein enzymes, recognize substrates based upon a precise complementary shape, charge and hydrophilic/hydrophobic interactions with its active site. Therefore, Applicants query why one of ordinary skill in the art using eukaryal tRNA endonucleases would look to Santoro & Joyce when eukaryal tRNA endonucleases do not have the same binding characteristics or catalytic mechanism as DNAzymes?

In addition, Santoro & Joyce disclosed that its DNAzymes require a bulge-helix-loop (BHL; *see* FIG. 2, left side of figure) or loops (*see* FIG. 2, right side of figure). BHLs and loops, however, are not the same as BHBs. *See*, FIG. 1 of the application. In fact, Fabbri *et al.* disclosed that eukaryal tRNA endonucleases cleaved BHLs very inefficiently. *See*, p. 265, 2nd to 3rd column of Fabbri *et al.* Therefore, Applicants again query why one of ordinary skill in the art using eukaryal tRNA endonucleases would look to Santoro & Joyce when eukaryal tRNA endonucleases do not cleave BHLs efficiently and do not cleave loops at all?

Moreover, Santoro & Joyce disclosed that cleavage with DNAzymes occurred in only one strand and that such cleavage was not even within the BHL or the loop. In contrast, both Fabbri *et al.* and this application disclose that cleavage with eukaryal tRNA endonucleases is double-stranded and occurs in both bulges of the BHB. Therefore, Applicants once again query why one of ordinary skill in the art using eukaryal tRNA endonucleases would look to Santoro & Joyce when eukaryal tRNA endonucleases have double-stranded cleavage and cleave a structure that is distinct from DNAzymes?

From the statements made in the Office Action, the Examiner appeared to simply pick and choose from Santoro & Joyce only so much of it as will support a given position, to the exclusion of other parts necessary to the full appreciation of what the document fairly suggests to one of ordinary skill in the art. This kind of examination is improper, as an obviousness inquiry under 35 U.S.C. § 103 should look at whether the claimed invention as a whole would have been

obvious, not whether the differences themselves would have been obvious. *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 218 USPQ 871 (Fed. Cir. 1983); and *Bausch & Lomb, Inc. v. Barnes-Hind/Hydrocurve, Inc.*, 796 F.2d 443 (Fed. Cir. 1986).

It is nothing more than pure coincidence that the dinucleotide sequence, UA, may be cleaved by the DNAzymes of Santoro & Joyce, as well as by eukaryal tRNA endonucleases. Interestingly, both DNAzymes in Santoro & Joyce have a at least one dinucleotide sequence of GA in the BHL or the loop. *See* FIG. 2 of Sanatoro & Joyce. Curiously, the DNAzymes of Santoro & Joyce did not cleave GA in the BHL or the loop, which is cleaved by eukaryal tRNA endonucleases. Conveniently, the Examiner did not address this point in the Office Action. As such, one of ordinary skill in the art would be unlikely to look to Santoro & Joyce to elucidate a method of cleaving non-tRNA molecules with eukaryal tRNA endonucleases. Likewise, it would not have been obvious to one of ordinary skill in the art to cleave BHBs created with two RNA molecules by eukaryal tRNA endonucleases, especially since the eukaryal tRNA endonucleases do not recognize their substrate based upon Watson-Crick base pairing. In view of the amendments noted above and the remarks presented herein, Applicants respectfully request reconsideration of this rejection as applied to Claims 1-11.

With respect to Claims 12-17, Applicants acknowledge that Fabbri *et al.* disclosed that archaeal tRNA endonucleases can process pre-tRNAs having a BHB. In addition, Fabbri *et al.* emphasized the importance of pre-tRNA secondary structure in the target RNA molecule (*see, e.g.*, FIG. 1), but it did not contemplate or disclose that archaeal tRNA endonucleases could cleave non-tRNA molecules. As noted above, the pending claims specifically recite that the target molecule does not comprise a tRNA structure. Moreover, Applicants amend Claim 12 to recite that the BHB is obtained by hybridizing the target RNA with a second RNA designed to form a BHB (*i.e.*, trans-formed BHB). Fabbri *et al.* did not contemplate or disclose trans-formed BHBs.

More importantly, Fabbri *et al.* did not contemplate or disclose that one of ordinary skill in the art could use archaeal tRNA endonucleases to create fusion proteins in heterologous systems. Fabbri *et al.* only disclosed cleavage of pre-tRNA by tRNA endonucleases in *in vitro* conditions that did not involve cells. In contrast, the application discloses that one of ordinary skill in the art can obtain a chimeric RNA molecule with tRNA endonucleases that can be translated into a fusion protein. *See, e.g.*, FIGS. 4-7 of the application. Applicants were the first

to appreciate that heterologous archaeal tRNA endonucleases could cleave target RNA, and then an endogenous ligase could subsequently ligate cleavage products from the target RNA and a second RNA to produce a fusion RNA having at least one cleavage product from the first target RNA molecule and at least one cleavage product from the second target RNA molecule. This link was previously unknown in the art; therefore, Applicants are entitled such a claim.

As noted above, Santoro & Joyce is a flawed document. While Applicants again acknowledge that Santoro & Joyce disclosed DNAzymes, these DNAzymes are structurally and functionally distinct from archaeal tRNA endonucleases, which are protein enzymes. Santoro & Joyce did not contemplate or disclose using its DNAzymes to create fusion proteins in heterologous systems. Santoro & Joyce only disclosed cleavage of oligonucleotides by DNAzymes in *in vitro* conditions that did not involve cells. In addition, Santoro & Joyce only disclosed single-stranded cleavage, which does not provide the proper 5' and 3' ends for ligation to create a fusion RNA. Moreover, Santoro & Joyce did not disclose cleavage within the BHL or the loop. In contrast to Santoro & Joyce, the pending claims specifically recite that cleavage occurs within the second and third nucleotides at the bulges (and is necessarily double-stranded). Given these significant differences, Applicants query why one of ordinary skill in the art using archaeal tRNA endonucleases would look to Santoro & Joyce? As such, it would not have been obvious to one of ordinary skill in the art to cleave BHBs created with two RNA molecules by archaeal tRNA endonucleases and subsequently ligate the cleavage products to create a fusion RNA.

Again, the Examiner appeared to simply pick and choose from Santoro & Joyce only so much of it as will support a given position, to the exclusion of other parts necessary to the full appreciation of what the document fairly suggests to one of ordinary skill in the art. As noted above, this type of examination is improper and cannot be used to reject claims under 35 U.S.C. § 103. In view of the amendments noted above and the remarks presented herein, Applicants respectfully request reconsideration of this rejection as applied to Claims 12-17.

Rejections Under 35 U.S.C. § 101

The Examiner provisionally rejected Claims 12-17 as claiming the same invention as Claims 12-17 of US Patent Application No. 10/296,574. Because this is only a provisional rejection, Applicants believe that no response is required at this time.

Additional Remarks

Applicants cancel Claims 2-3 because the content of each is now incorporated into amended Claim 1. Applicants also amend Claim 12 to correct a typographical error – "archeael" is now "archaeal." Applicants also amend Claim 7 in view of the amendments made to Claim 1 that incorporated part of the limitation previously set forth in Claim 7. Likewise, Applicants amend Claim 13 in view of the amendments made to Claim 12 that incorporated part of the limitation previously set forth in Claim 13. Moreover, Applicants amend Claim 14 so that its language is consistent with that in Claim 12.

Fees

A petition for a three-month extension of time accompanies this Response so that it will be deemed to have been timely filed. No other extension of time is believed due, but should any additional extension be due, in this or any subsequent response, please consider this to be a petition for the appropriate extension, and a request to charge the extension fee to Deposit Account No. 17-0055.

Respectfully submitted,

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